

United States Court of Appeals

FOR THE DISTRICT OF COLUMBIA CIRCUIT

Argued February 1, 1999 Decided July 16, 1999

No. 98-5151

Pfizer Inc.,
Appellant

v.

Donna E. Shalala, Secretary,
U.S. Department of Health and Human Services, et al.,
Appellees

Appeal from the United States District Court
for the District of Columbia
(No. 97cv01554)

Bert W. Rein argued the cause for appellant. With him on the briefs were Andrew S. Krulwich, Bruce G. Joseph and Michael L. Sturm.

Drake Cutini, Attorney, U.S. Department of Justice, argued the cause for appellees. With him on the brief was

Frank W. Hunger, Assistant Attorney General. Gerald C. Kell, Attorney, entered an appearance.

E. Anthony Figg argued the cause for appellee Mylan Pharmaceuticals, Inc. With him on the brief was Steven Lieberman.

David G. Adams was on the brief for appellee Penwest Pharmaceuticals Group. David M. Malone and Lawrence B. Bernard entered appearances.

David F. Weeda and David L. Durkin were on the brief for amicus curiae National Association of Pharmaceutical Manufacturers.

Before: Edwards, Chief Judge, Ginsburg, and Tatel, Circuit Judges.

Opinion for the Court filed by Circuit Judge Ginsburg.

Ginsburg, Circuit Judge: Pfizer, Inc. manufactures and sells the pioneer drug Procardia XLR, which contains the active ingredient nifedipine, a calcium-blocker used to treat angina and hypertension. Procardia XLR uses a patented "osmotic pump" to control the extended release of nifedipine. Mylan Pharmaceuticals, Inc. filed an abbreviated new drug application (ANDA) with the Food and Drug Administration seeking approval of its own extended release nifedipine product as a generic "pharmaceutical equivalent" to Procardia XLR; Mylan's product, however, uses an extended release mechanism different from Pfizer's osmotic pump. Despite the different mechanisms the FDA accepted Mylan's ANDA for processing but has not yet decided whether to approve it.

Pfizer claims, as it did in a so-called "citizen petition" filed with the FDA before Mylan had sought approval for its drug, that the osmotic pump is a unique "dosage form." 21 U.S.C. s 355(j)(2)(A)(iii). It therefore follows, according to Pfizer, that the FDA must reject Mylan's ANDA. The FDA and intervenors Mylan and Penwest Pharmaceuticals Group, which developed the extended release mechanism used in Mylan's drug, argue that the agency's decision is not ripe for

judicial review. For the reasons below, we agree with the agency and dismiss Pfizer's petition for review.

I. Background

A. Statutory and Regulatory Framework

The approval of the FDA is required before any drug may be marketed in the United States. See 21 U.S.C. s 355(a). The sponsor of a new drug ordinarily must undertake expensive and time-consuming clinical (that is, human) studies in order to show that its new drug is safe and effective for its intended use. See id. s 355(b). Once the FDA approves a new drug, however, a competitor seeking to market a generic version may file an ANDA, relying upon the clinical findings the FDA has already approved with respect to the pioneer drug. See id. s 355(j).

In order to gain approval of an ANDA, an applicant must show that its generic drug is "bioequivalent to the listed [pioneer] drug." Id. s 355(j)(4)(F). Bioequivalence refers generally to the rate at which, and the extent to which, the body absorbs the active ingredient(s) in the drug. See id. s 355(j)(8); 21 C.F.R. s 320.1(e).

To gain approval as a "pharmaceutical equivalent," 21 C.F.R. s 320.1(c), an applicant must additionally "show that the active ingredient ..., the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed [pioneer] drug." 21 U.S.C. s 355(j)(2)(A)(ii)-(iii); see also id. s 355(j)(4)(C)-(D). If the generic drug differs from the pioneer drug in any of those four respects, then the manufacturer may still avail itself of the ANDA process by filing a "suitability petition," see id. s 355(j)(2)(C), upon the basis of which its product could be approved as a "pharmaceutical alternative" to the pioneer drug. 21 C.F.R. s 320.1(d). The distinction is significant because many states permit only a pharmaceutical equivalent to be substituted for the pioneer drug, and Medicaid and many insurance plans do not reimburse patients for the cost of a pharmaceutical alternative.

The FDA first reviews an ANDA (whether submitted for approval as a pharmaceutical equivalent or as a pharmaceutical alternative) in order to determine whether it may be "received," i.e., accepted for processing, for which the standard is that "the abbreviated application is sufficiently complete to permit a substantive review." Id. s 314.101(b)(1); see also id. (d)(3) (FDA may reject ANDA if incomplete "on its face"). If, upon substantive review, the FDA finds the generic drug satisfies all of the applicable statutory requirements, then it must approve the ANDA. See 21 U.S.C. s 355(j)(4).

The FDA publishes a current list of all approved drugs, known as the "Orange Book." See U.S. Dep't of Health & Human Serv., Approved Drug Products With Therapeutic Equivalence Evaluations (17th ed. 1997). In an appendix to the Orange Book the FDA lists 74 dosage forms. Among these are aerosols, implants, capsules, and seven types of tablets, including chewable, dispersible, effervescent, and the one with which we are concerned, "extended release."

B. Pfizer's Claims

The FDA approved Pfizer's new drug application for Procardia XLR in 1989 and listed it in the 1990 Orange Book as having the dosage form "tablet, extended release; oral." As mentioned, the extended release mechanism in Procardia XLR is a patented osmotic pump. As fluid from the gastrointestinal tract enters the shell of the tablet, it dissolves the active ingredient, nifedipine, and causes a "push" layer to swell, thereby gradually expelling the nifedipine into the gastrointestinal tract through a hole in the shell. Compl. p 20.

In 1993 Pfizer filed a "citizen petition" with the FDA, pursuant to 21 C.F.R. s 10.30, asking the agency to recognize Pfizer's "oral osmotic pump [as] a distinct dosage form." Pfizer also contended the agency must require a suitability petition if a generic drug "uses a different mechanism of release from the reference drug."

The FDA had not ruled upon Pfizer's petition when, nearly four years later, Mylan submitted an ANDA for an extended release nifedipine tablet claiming pharmaceutical equivalence to Procardia XLR. The FDA accepted Mylan's application for processing even though its tablet uses a different extended release mechanism than does Procardia XLR.

After failing to persuade the agency to stay or to withdraw its acceptance of Mylan's ANDA, Pfizer filed this suit in the district court challenging that acceptance as arbitrary, capricious, and contrary to law. In a second count Pfizer repeated the claim, first made in its still-pending citizen petition, that the FDA was obliged to recognize its osmotic pump as a distinct dosage form. Shortly thereafter the FDA denied Pfizer's citizen petition.

The district court held that Pfizer's challenge to the FDA's receipt of Mylan's application was unripe because the agency had not yet decided whether to approve Mylan's generic drug. See *Pfizer Inc. v. Shalala*, 1 F. Supp. 2d 38, 44 (1998). On the other hand, the court held that the FDA's denial of Pfizer's citizen petition was "final agency action," and therefore ripe for review. *Id.* On the merits of that claim, the district court upheld as rational and consistent with the statute the FDA's refusal to treat Pfizer's osmotic pump as a distinct form of dosage. See *id.* at 44-48.

II. Analysis

The FDA contends that neither its acceptance of Mylan's ANDA for processing nor its denial of Pfizer's citizen petition caused Pfizer injury sufficiently imminent to confer jurisdiction upon the court. Pfizer responds that it is "imminently threatened with economic injury from unlawful competition." So are Pfizer's claims ripe for judicial review or not?

Here is what the Supreme Court said last Term by way of summarizing the ripeness doctrine. In order to determine whether a controversy is ripe a court must "evaluate both the fitness of the issues for judicial decision and the hardship to the parties of withholding court consideration." *Texas v. United States*, 523 U.S. 296, 301 (1998). "A claim is not ripe

for adjudication if it rests upon contingent future events that may not occur as anticipated, or indeed may not occur at all." *Id.* at 300. Thus, the ripeness requirement serves "to prevent the courts, through avoidance of premature adjudication, from entangling themselves in abstract disagreements over administrative policies, and also to protect the agencies from judicial interference until an administrative decision has been formalized and its effects felt in a concrete way by the challenging parties." *Ohio Forestry Ass'n v. Sierra Club*, 523 U.S. 726, 732-33 (1998) (quoting *Abbott Labs. v. Gardner*, 387 U.S. 136, 148-49 (1967)).

We assess first Pfizer's challenge to the FDA's acceptance of Mylan's ANDA for processing. Pfizer claims the agency's action is final and therefore fit for review because once having decided, based upon the information contained in Mylan's application, that Mylan's drug uses the same dosage form as Procardia XLR, the FDA will not "alter its views with respect to the necessity of Mylan filing a suitability petition." The decision to accept Mylan's ANDA for processing as a pharmaceutical equivalent to Procardia XLR is, however, merely the first step in the agency's approval process. The critical fact remains that the FDA may never approve Mylan's application--whether because it decides in the end that the dosage form of Mylan's drug is different from that of Procardia XLR or for some entirely different reason, such as a lack of bioequivalence. Therefore, "depending upon the agency's future actions ... review now may turn out to have been unnecessary" and could deprive the agency of the opportunity to apply its expertise and to correct any mistakes it may have made. *Id.* at 736 (holding challenge to agency's logging plan unripe when no specific area was yet identified for harvesting and agency might revise or modify plan).

Pfizer contends the FDA's own regulations demonstrate that it does not consider its acceptance of an ANDA for processing to be a "tentative" decision because it gives the first person to file a generic application (here Mylan) a 180-day marketing priority as against any later-filed generic application. See 21 C.F.R. s 314.107(c). In other words,

says Pfizer, the agency's acceptance of Mylan's ANDA "affects the legal rights of all subsequent applicants referencing Procardia XLR." We find this argument doubly unpersuasive. First, it assumes its own conclusion, for Mylan will get the 180-day marketing priority only if its application is finally approved. Second, the legal rights that will be affected are not Pfizer's but those of its competitors, about which Pfizer is not in a position to complain.

Nor can Pfizer point to any imminent hardship arising from the FDA's acceptance of Mylan's ANDA. Before Pfizer could suffer its claimed "economic injury from unlawful competition," FDA approval for a pharmaceutical equivalent to Procardia XLR would have to be not only sought but granted. That has not happened. Therefore "no irreparable adverse consequences flow from requiring a later challenge." *Toilet Goods Ass'n v. Gardner*, 387 U.S. 158, 164 (1967). This case might nonetheless be ripe if the FDA's acceptance of Mylan's ANDA for processing somehow foreclosed Pfizer's right ever to get meaningful judicial review, but it does not. If the FDA eventually approves Mylan's application, Pfizer may then challenge the reasons underlying its final decision, including the agency's interpretation of the statutory term "dosage form."

Pfizer next suggests that the agency's acceptance of Mylan's ANDA for processing compelled it to sue Mylan for patent infringement and thereby to incur the burden of litigation expenses. Not so. Pursuant to the Drug Price Competition and Patent Term Restoration Act of 1984, which established the ANDA procedure, see Pub. L. No. 98-417, 98 Stat. 1585, the owner of a pioneer drug may, by suing the sponsor of the ANDA for patent infringement, cause the FDA to stay its approval of a generic drug for 30 months. See 21 U.S.C. s 355(j)(5)(B)(iii). To get the benefit of the stay, such a suit must be filed within 45 days after the owners of the pioneer drug and of any associated patents receive notice from the sponsor of the ANDA claiming that the pioneer's patents are either "invalid or will not be infringed" by the generic drug. *Id.* s 355(j)(2)(A)(vii)(IV). Nothing in the Act, however, precludes the owner of a pioneer drug from waiting

longer than 45 days to sue for patent infringement. Therefore, Pfizer voluntarily incurred the expense of preemptive patent litigation in order to get a substantial statutory benefit, namely, a stay of the FDA's approval of Mylan's ANDA. In sum, Pfizer suffers no hardship because it "is not required to engage in, or to refrain from, any conduct." *Texas*, 523 U.S. at 301. We therefore hold the FDA's acceptance for processing of Mylan's ANDA is not ripe for judicial review at this time.

If the FDA's acceptance of Mylan's ANDA is not ripe, then it follows a fortiori that the FDA's denial of Pfizer's citizen petition is not ripe. Pfizer raises precisely the same objection to both agency actions, namely, that the FDA erred in interpreting the statutory term "dosage form." But in denying Pfizer's citizen petition, the FDA did not apply that interpretation to a particular set of facts, as it did in accepting Mylan's ANDA for processing. Rather, it simply refused to affirm the negative proposition that no other extended release mechanism could ever be deemed under the statute to constitute the same dosage form as Pfizer's osmotic pump. Therefore Pfizer's challenge to the agency's refusal to recognize its osmotic pump as a unique dosage form raises just the sort of abstract disagreement over an administrative policy at which the ripeness doctrine is aimed. See *Ohio Forestry*, 523 U.S. at 736. "Here, as is often true, determination of the scope of legislation in advance of its immediate adverse effect in the context of a concrete case involves too remote and abstract an inquiry for the proper exercise of the judicial function." *Texas*, 523 U.S. at 301.

Pfizer defends its ground by pointing to an FDA regulation that deems the agency's response to a citizen petition a "final agency action ... reviewable in the courts," 21 C.F.R. s 10.45(d); but a final agency action nonetheless can be unripe for judicial review. See *Mount Wilson FM Broad. v. FCC*, 884 F.2d 1462, 1465 (D.C. Cir. 1989). Ripeness entails a functional, not a formal, inquiry. An administrative agency, which is not subject to Article III of the Constitution of the United States and related prudential limitations, may issue a declaratory order in mere anticipation of a controversy or

simply to resolve an uncertainty. See Metropolitan Council of NAACP Branches v. FCC, 46 F.3d 1154, 1161 (D.C. Cir. 1995). An Article III court, however, may not adjudicate a dispute until it has both crystallized as an actual "case or controversy" and satisfied the prudential requirements of the ripeness doctrine. See Reno v. Catholic Social Servs., Inc., 509 U.S. 43, 57 n.18 (1993) (explaining "ripeness doctrine is drawn both from Article III limitations on judicial power and from prudential reasons for refusing to exercise jurisdiction").

* * *

After oral argument of this case the FDA tentatively approved Mylan's ANDA. The agency conditioned its final approval upon both the expiration of the 30-month period established in 21 U.S.C. s 355(j)(5)(B)(iii), during which the agency is prohibited from approving Mylan's new drug, and assurance from Mylan that there is no new information affecting whether final approval should be granted. Pfizer argues that this development ripens its challenge to the FDA's acceptance of Mylan's application for processing because the agency contemplates no additional substantive analysis of Mylan's application. See Regional Rail Reorganization Act Cases, 419 U.S. 102, 140 (1974) (holding that "since ripeness is peculiarly a question of timing, it is the situation now rather than the situation at the time of the District Court's decision that must govern").

We agree, however, with the FDA's contention that Pfizer's challenge is still unripe. Although it is now more likely that the FDA will eventually approve Mylan's drug, the agency's tentative approval causes Pfizer no hardship at present or in the near future, nor does it render Pfizer's challenge fit for review. See Texas, 523 U.S. at 300 (holding case unripe even assuming greater certainty of adverse action resting upon future contingent events).

As to hardship, nothing untoward can happen to Pfizer until at least December 1999, when the 30-month period triggered by the filing of its patent suit against Mylan expires

and the FDA (assuming no change of circumstances) may issue a final approval.* As to fitness, should we dismiss as unripe Pfizer's present challenge to the FDA's acceptance for processing of Mylan's ANDA, then Pfizer could not only renew that claim, which is based solely upon the FDA's interpretation of the statutory dosage form requirement, it could also bring in the same action any other claim that may arise from the agency's final approval--if and when it is given--such as lack of bioequivalence. Accordingly, judicial intervention at this time could lead to "piecemeal review which at the least is inefficient and upon completion of the agency process might prove to have been unnecessary." *FTC v. Standard Oil Co.*, 449 U.S. 232, 242 (1980).

III. Conclusion

We hold that Pfizer's challenges to the FDA's acceptance for processing of Mylan's ANDA and to its denial of Pfizer's citizen petition are both unripe for review. The judgment of the district court is therefore

Affirmed in part and reversed in part.

* Neither party claims there is any likelihood that the patent suit will be dismissed or settled at an earlier date.